generalized urticaria, sneezing, tearing, coughing, wheezing, and even anaphylaxis with hypotension shortly after exposure to latex products. Some investigators have noted a progression of symptoms in health care workers from contact dermatitis to localized urticaria to systemic IgE-related symptoms. On the other hand, a significant number of patients who develop systemic IgE symptoms do so without any preexisting contact dermatitis.

In a patient known to have other allergies, it can be difficult to determine whether latex exposure is precipitating symptoms or simply aggravating them. In questionnaires, many people self-report symptoms that could be from latex exposure, but few cases are confirmed by diagnostic tests. Recent epidemiologic studies have reported prevalence rates in health care workers ranging from 2.9 to 17%, but ascertainment bias may be a factor in those results. Better-designed epidemiologic studies as well as longitudinal studies must be undertaken.

The immunologic mechanism for systemic reactions to latex is a type I hypersensitivity mediated by IgE antibodies directed against latex rubber proteins. According to one study, 57 of the 200 proteins in latex bind to human IgE. Seven sensitizing latex proteins have been identified, cloned or partially characterized, and assigned allergen designations of Hev b1–b7 by the International Union of Immunological Societies. A high percentage of patients who are latex sensitive are also positive for at least one food skin test, suggesting epitopes common to both latex and food allergens. Foods that cause allergic reactions in latex-sensitive patients include banana, avocado, kiwi, chestnut, potato, cherry, apricot, papaya, passion fruit, and melon.

Three FDA-approved latex-specific IgE in vitro tests are available: Alastat, CAP, and Hycor. Although these assays claim high sensitivity and specificity, their accuracy and reliability can only be determined with broader clinical experience in various populations. A challenge procedure may be used to clarify the diagnosis in patients who have clinical histories that conflict with skin test or in vitro test results, and developing standardized challenge procedures is an important area of research. There is no standardized skin test reagent—testing patients with extracts of unknown potency has resulted in systemic reactions, limiting the use of skin testing. A multicenter clinical trial using a Food and Drug Administration–approved non-ammoniated latex extract is underway.

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Antileukotrienes—1997 and Beyond

Antileukotrienes represent a new class of asthma medication. They modulate inflammation, they have a mild bronchodilator activity, and their virtual lack of side effects represents an advantage over many other antiasthmatic compounds. Antileukotrienes have the ability to counter most of the basic pathogenic mechanisms of asthma, and they modify increased vascular permeability and edema formation, increased mucus production, bronchoconstriction, and cellular inflammatory exudate.

Two main classes of agents modulate leukotrienes, the leukotriene receptor antagonists and the inhibitors of key enzymes involved in the synthesis of leukotrienes. The latter class can be divided into two further groups: those that inhibit 5-lipoxygenase [5-LO] and those that inhibit the activity of 5-lipoxygenase activating protein (FLAP). Of the many compounds currently under study, only two agents, zafirlukast and zileuton, have received approval from the Food and Drug Administration (FDA).

The potential usefulness of the antileukotrienes has been demonstrated in various experimental and clinical studies. Their mechanisms vary, suggesting that agents within the leukotriene category should be substituted if clinical response is not adequate. For example, virtually all the receptor agonists improve dose response, and some agents, such as zafirlukast and the FLAP inhibitor BAY 10005, block both early- and late-phase allergen challenges.

Many agents block hyperresponsiveness as measured by methacholine or histamine inhalation challenge. They include the receptor antagonists zafirlukast and pranlukast and the synthesis inhibitors BAY 10005 and MK-886. Almost all of the leukotriene antagonists and inhibitors have been shown to block exercise-induced asthma and cold air challenge to some degree.

It is thought that antileukotrienes might be particularly effective in the subgroup of patients with aspirin idiosyncrasy. The leukotriene antagonist SKF-104353 was shown to be an effective blocker in five subjects studied; similarly, pranlukast in a single dose of 225 mg showed an impressive effect in six aspirin-sensitive patients. A single dose of 750 mg of montelukast blocked an inhaled lysine aspirin challenge in patients with aspirin sensitivity, and zileuton in a dose of 600 mg four times a day for 6 to 8 days also was found to attenuate aspirin challenges and decrease urinary LTE_4 levels. In the latter study, the agent was also found to attenuate nasal, gastrointestinal, and dermal responses to aspirin.

Many researchers have studied antileukotrienes in clinical asthma. For example, compared with baseline measurements, patients receiving 40 mg of zafirlukast experienced a 46% decrease in nighttime awakening, a 30% decrease in albuterol use, and a 26% improvement in daytime symptoms. The oral compound MK-571 has also been found to improve asthma symptoms and pulmonary function and decrease beta-agonist use. Verlukast has shown similar effects, as have montelukast, pranlukast, and zileuton.

In general, the antileukotriene agents are very safe. Earlier agents that caused significant elevations of liver function tests are no longer manufactured, but some concerns regarding liver function remain. Zileuton ingestion has been associated with mild and transient elevation of liver enzymes that generally reverts to normal with continued therapy or cessation. The FDA has suggested that monitoring be done monthly for the first few months, and periodically thereafter. Churg-Strauss syndrome has been found in association with zafirlukast when corticosteroid anti-inflammatory therapy was being tapered. Thus asthma patients in whom corticosteroid therapy is being reduced should be carefully monitored. Adrenal suppression and cataracts have been mentioned as potential side effects; further study is required.

Antileukotrienes are currently recommended for mild persistent asthma by the National Heart, Lung and Blood Institute, and they may be effective in other subgroups of asthma.

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Combination Therapy for HIV Disease

As a result of recent advances, the treatment of HIV disease is now firmly based on HIV immunopathogenesis and viral dynamics. This paradigm shift—along with new, potent anti-retroviral drugs, a better understanding of drug resistance, and the ability to monitor viral load—has engendered updated recommendations for anti-retroviral therapy.

The concept of virologic latency after primary HIV infection is no longer tenable. HIV immunopathogenesis reveals that viral replication and clearance, as well as $CD4^+$ cell destruction and replacement, are rapid, continuous, high-level processes at all stages of the disease. Estimates suggest that 10 billion virions and 2 billion $CD4^+$ cells are produced and destroyed each day, and that the plasma virus half-life is only 6 hours. More than 99 percent of plasma viremia results from these ongoing cycles of infection in $CD4^+$ lymphocytes. Eventually, the immune system is overwhelmed by the unrelenting assault.

HIV infects multiple cellular compartments. Actively productive $CD4^+$ cells with short half-lives make up the first compartment, the major reservoir of virus in the body. A second compartment of longer-lived tissue macrophages and follicular dendritic cells accounts for 1% of the viral burden. A third compartment of chronically infected cells may exist (perhaps in the brain and cerebral spinal fluid), offering proviral DNA a long-term, possibly life-long, sanctuary site. The mathematical model for eradication of HIV suggests that complete viral suppression for a period of 2 to 3 years may eradicate the virus from the host in the first two compartments, but a risk of relapse remains from the sanctuary sites.

The ability to quantitate the level of HIV-1 RNA in the plasma (viral load) has been essential to our increased understanding of viral pathogenesis and anti-retroviral efficacy. Viral load is a practical and reliable marker of disease progression and treatment benefit.

Recent data has demonstrated a strong relationship between viral load and clinical outcomes. Natural history studies have demonstrated that baseline viral loads predict over a 10-year period of observation the rate of $CD4^+$ T-lymphocyte decline, the time to AIDS, and the time to death from AIDS. Similarly, clinical trials of nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors have consistently shown a strong correlation between reductions in viral load and reduced risk of $CD4^+$ T-cell decline, AIDS, or death from AIDS.

Within the past year, five new drugs have been approved for the treatment of HIV-1 infection: two nonnucleoside reverse transcriptase inhibitors (nevirapine and delavardine) and three protease inhibitors (ritonavir, indinavir, and nelfinavir). The addition of these agents has resulted in a growing number of potent virus-suppressing combination regimens. The term "highly active anti-retroviral therapy" (HAART) has been coined to describe these new, very effective, combinations.

The promise of these new combinations notwithstanding, it has become clear that the development of drug resistance remains the Achilles heel of anti-retroviral therapy. A new generation of HIV is produced in 2.6 days, yielding 140 generations per year. Assuming 10 billion replicative cycles per day, every possible mutation in the HIV genome can occur several times a day. Consequently, if HIV replication is not completely arrested, mutants will rapidly arise. Genotypic and phenotypic laboratory assays for drug resistance are in development.

Potent anti-retroviral combination regimens initiated in moderately advanced disease have demonstrated impressive immunologic, virologic, and clinical responses. The immunologic response is incomplete, however, with respect to full restoration of $CD4^+$ cell number and function, thus arguing in favor of earlier intervention.

The mantra of HIV therapy has become "hit early, hit hard." Significant scientific rationale exists for the new, more aggressive goal of suppressing HIV replication as completely as possible throughout the entire course of infection. Powerful, theoretical rationale exists as well for intervening as early as possible in the course of HIV disease to avoid irreversible immune deficits. Highly